PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

TABUSHI, Eiji
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome
Yodogawa-ku, Osaki-shi
Osaka 532-8514
JAPON

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 03 November 2000 (03.11.00)	
Applicant's or agent's file reference PWO-20205	**IMPORTANT NOTIFICATION**
International application No. PCT/JP00/05731	International filing date (day/month/year) 24 August 2000 (24.08.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 31 August 1999 (31.08.99)
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
31 Augu 1999 (31.08.99)	11/244250	JP	13 Octo 2000 (13.10.00)

The International Bureau of WIPO **34, chemin d s Col mbettes** **1211 Geneva 20, Switz rland**	Authorized officer Khemais BRAHMI
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/304 (July 1998)

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
TABUSHI, Eiji
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome
Yodogawa-ku, Osaki-shi
Osaka 532-8514
JAPON

Date of mailing (day/month/year) 08 March 2001 (08.03.01)		
Applicant's or agent's file reference PWO-20205		**IMPORTANT NOTICE**
International application No. PCT/JP00/05731	**International filing date** (day/month/year) 24 August 2000 (24.08.00)	**Priority date** (day/month/year) 31 August 1999 (31.08.99)
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EA,EE,EP,ES,FI,GB,GD,GE,GH,
   GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,
   PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   08 March 2001 (08.03.01) under No. WO 01/15525

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

3871376

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PWO-20205	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP00/05731	International filing date (*day/month/year*) 24 August 2000 (24.08.00)	Priority date (*day/month/year*) 31 August 1999 (31.08.99)
International Patent Classification (IPC) or national classification and IPC A01N 1/02, C07D 487/04		
Applicant FUJISAWA PHARMACEUTICAL CO., LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 21 February 2001 (21.02.01)	Date of completion of this report 10 August 2001 (10.08.2001)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIM[redacted]RY EXAMINATION REPORT

International application No.
[redacted]PCT/JP00/05731

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP 00/05731

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-6	NO
Industrial applicability (IA)	Claims	1-6	YES
	Claims		NO

2. Citations and explanations

Document 1: R. T. Currin et al., "Protection by Carolina rinse solution, acidotic pH and glycine against lethal reperfusion injury to sinusoidal endothelial cells of rat livers stored for transplantation", Transplanation, 1996, Vol. 62, No. 11, pp. 1549-1558

Document 2: T. Oida et al., "The effect of N-monomethyl-L-arginine (L-NMMA) on orthotopic liver transplantation in rats", Nichidai Igaku Zasshi, 1995, Vol. 54, No. 12, pp. 745-50

Document 3: JP, 06-502178, A (Fujisawa Pharmaceutical Co., Ltd.), 10 March 1994 (10.03.94) & WO, 92/12154, A1

Document 4: EP, 531901, A2 (Fujisawa Pharmaceutical Co., Ltd.), 17 March 1993 (17.03.93) & EP, 531901, A3 & US, 5356897, A & CA, 2077732, A1 & CN, 1070404, A & HU, 65204, A & JP, 06-287188, A & JP, 07-0888386, B2 & US, 5478827, A & JP, 07-252256, A & US, 5624931, A

Document 5: US, 5670503, A (Fujisawa Pharmaceutical Co., Ltd.), 23 September 1997 (23.09.97) & CN, 1120840, A & JP, 08-507056, A & EP, 686156, A1 & WO, 94/19350, A1 & IL, 108562, A & CA, 2156919, A1 & AU, 681625, B & HU, 70832, A

[1] Claims 1 and 2 do not involve an inventive step in the light of Document 1 cited in the international search report.

Document 1 discloses the organ preserving effect of CRS (Carolina rinse solution) and given the disclosure that a depression of TNF-α was observed with CRS, Document 1 suggests that CRS, with its suppressing effect on α-TNF production, is effective as an organ preserving agent (see especially page 1556, Table 6). Therefore, a person skilled in the art could easily conceive of adopting said constitutional feature.

[2] Claims 1 and 2 do not involve an inventive step in the light of Document 2 cited in the international search report.

Document 2 indicates that an enzyme induced by TNF-α causes NO production and interferes with organ preservation. Document 2 also discloses an organ preserving effect of NMMA (N-monomethyl-L-arginine), and given the mention that a depression of TNF-α was observed after administering NMMA, suggests that NMMA, with its suppressing effect on production α-TNF, is effective as an organ preserving agent (see especially pages 748-749). Therefore, a person skilled in the art could easily conceive of adopting said constitutional feature.

[3] Claim 3 does not involve an inventive step in the light of Documents 1 and 2 and Document 3 cited in the international search report.

See [1] and [2] above.

Document 3 discloses imidazotriazine derivatives represented by the formula set forth in Claim 3, as inhibitors of TNF production (see page 5, upper left

column, line 3 to upper right column, line 7).

Since it is known that TNF-α interferes with organ preservation, a person skilled in the art could easily conceive of using an aforementioned imidazotriazine derivative as an organ-preserving agent.

[4] Claim 4 does not involve an inventive step in the light of Documents 1 and 2 and Document 4 cited in the international search report.

See [1] and [2] above.

Document 4 discloses pyrazole derivatives represented by the formula given in Claim 4, as inhibitors of TNF production (see page 3, lines 1-53).

Since it is known that TNF-α interferes with organ preservation, a person skilled in the art could easily conceive of using an aforementioned pyrazole derivative as an organ-preserving agent.

[5] Claims 5 and 6 do not involve an inventive step in the light of Documents 1 and 2 and Document 5 cited in the international search report.

See [1] and [2] above.

Document 5 discloses pyrazotriazine derivatives represented by the formulae presented in Claims 5 and 6, as inhibitors of TNF production (see especially column 1, line 10 to column 2, line 11).

Since it is known that TNF-α interferes with organ preservation, a person skilled in the art could easily conceive of using an aforementioned pyrazotriazine derivative as an organ-preserving agent.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The only "MAPK inhibitor", "interleukin-1-production inhibitor" or "tumour necrosis factor-production inhibitor" which is fully supported by the description as an organ-preserving agent is "7-(4-fluorophenyl)-2-phenyl-glyoxyloyl-8-(pydidine-4-yl)-1,2,3,4-tetrahydropyrazolo-[5,1-C][1,2,4]triazine", which is extremely restricted.